

1 DOCTOR LIPICKY: That's fine. I think that  
2 that's perfectly adequate, and I apologize for - but,  
3 we didn't have any way of doing it, basically. This  
4 is all IND information, and we haven't asked anyone  
5 permission to show anybody anything, an so on.

6 ACTING CHAIR BORER: Your apology is  
7 accepted.

8 3.3, Bosentan will affect the metabolism  
9 of many other drugs, and because of induction the  
10 effects will vary over time. This is a big issue that  
11 JoAnn has hit upon in her questions before.

12 Do you want to go through the issues here,  
13 please, JoAnn?

14 DOCTOR LINDENFELD: Yes. I think this is  
15 a big issue. I don't think that this influences  
16 approvability, but I do think that it requires  
17 probably a careful physician education program.

18 I believe that certainly, as I said  
19 before, that all the 3A4 inhibitors should be  
20 contraindicated at the present time, at least until  
21 you have some more data with bosentan. And, I think  
22 protein binding is less, but I think also physicians

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1        need to know what should we do about using other drugs  
2        that have some hepatotoxicity. We need some sort of  
3        list of those, or something to refer to, and then as  
4        we learn more about drugs excreted in the bile do we  
5        need to have a different monitoring program for that?

6                    And, it appears to me that we may, if  
7        there are other drugs that we know that have biliary  
8        excretion that patients may need to be followed more  
9        carefully on those drugs. I would, perhaps, get some  
10       additional advice from the rest of the panel or other  
11       experts.

12                   DOCTOR TEMPLE: Jeff, can I ask about that?  
13       Do you -- they presented the conclusion that a very  
14       potent 3A4 inhibitor, one of the antifungals, didn't  
15       increase -- it didn't increase the AOC by more than  
16       doubling it.

17                   DOCTOR LINDENFELD: Right, but they showed  
18       that cyclosporin acutely increases bosentan levels,  
19       about 30 fold, and that chronically it's --

20                   DOCTOR TEMPLE: Yeah, but cyclosporin  
21       doesn't work primarily that way. It's a transport  
22       protein inhibitor.

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1 DOCTOR LINDENFELD: Right.

2 DOCTOR TEMPLE: It's not primarily a 3A4  
3 inhibitor.

4 DOCTOR LINDENFELD: Right, but the  
5 ketoconazole was not tested acutely, so we just don't  
6 know.

7 DOCTOR TEMPLE: I couldn't hear that.

8 DOCTOR LINDENFELD: Ketoconazole wasn't  
9 tested acutely, so we don't know it's only a -

10 DOCTOR KORBIN: We did test it, we have  
11 data on day one, and again, it was only twice as much,  
12 not 30 times like you say.

13 DOCTOR LINDENFELD: You have data on day  
14 one?

15 DOCTOR KORBIN: Yes, and it was only twice  
16 as much.

17 DOCTOR LINDENFELD: Maybe, can you just  
18 comment on that for me, because that's not the data I  
19 got from the FDA.

20 ACTING CHAIR BORER: Can we have the  
21 microphone on, please? Why don't you come forward.

22 MR. WILLRUM: On a study submitted, we have

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1 data for a steady state bosentan concentrations. Day  
2 one interaction concentrations were not provided. I  
3 did not see them in the review.

4 DR. MONSUR: Here are the concentrations of  
5 bosentan, both given alone, the squares, and the  
6 concentrations of bosentan in the presence of  
7 concomitant administration of ketoconazole, right from  
8 the beginning of concomitant treatment, and you see  
9 all the way through the duration of the treatment, the  
10 concomitant treatment that we have, roughly, the two  
11 times increase in exposure, here expressed in the  
12 bosentan draft concentrations. And, this is in marked  
13 contrast to what we have seen with cyclosporin,  
14 indeed, there we see a 30-fold increase, but only in  
15 the beginning, the first dose effect, which dissipates  
16 a bit with time, but with ketoconazole we see  
17 completely different phenomenon.

18 So, it's not a pure 3A4 issue we are  
19 talking about. As Doctor Temple says, ketoconazole is  
20 the most potent 3A4 inhibitor we are aware of.

21 ACTING CHAIR BORER: Okay.

22 DOCTOR LINDENFELD: So, I still think we

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1 don't have evidence for erythromycin and ratinovir.

2 DOCTOR TEMPLE: We have usually thought  
3 that if you pass the ketoconazole test we are not too  
4 worried anymore, about erythromycin -

5 DOCTOR LINDENFELD: Okay.

6 DOCTOR TEMPLE: - and weaker 3A4  
7 inhibitors. That's, basically, the advice we give to  
8 people, test the worst case and then you are probably  
9 okay.

10 That's confounded by the transport  
11 inhibition problem, though.

12 DOCTOR LINDENFELD: Right, it is, and I  
13 think that's not the advice in the briefing booklet.

14 ACTING CHAIR BORER: Is it fair to say then  
15 that we have concern about drug/drug interactions, and  
16 that they haven't been fully explored, obviously,  
17 because of the limitation in population size, et  
18 cetera, and some kind of information to physicians  
19 about the lack of knowledge about this should be  
20 transmitted, and the need for caution, perhaps, in  
21 using drugs with similar metabolic pathways, is that  
22 a fair analysis?

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1 DOCTOR HIRSCH: I think that's the case,  
2 but let me just raise a question, which I can't answer  
3 for the panel, just to complete the discussion from  
4 earlier today. .

5 Are we looking for any additional  
6 pharmacokinetic information in this population from  
7 this sponsor, or are we satisfied with the current  
8 data that we have?

9 DOCTOR LINDENFELD: I think we'd like to  
10 see some in the younger ages. I think we talked about  
11 that earlier, we don't really have any oral data, we  
12 don't have any early data in PPH patients, but we  
13 believe the drugs differ a little bit in younger ages.

14 DOCTOR HIRSCH: Or, can we extrapolate from  
15 what's already known, which I think you implied? Are  
16 we satisfied?

17 DOCTOR KORBIN: Again, as I mentioned  
18 before, we have data on CHF patients, where we think  
19 it's the same. We do have some data now from children  
20 that we will be glad to share with the Agency, we  
21 didn't share it with the Agency yet, and it looks the  
22 same as we have seen in CHF patients.

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1 DOCTOR LINDENFELD: Okay.

2 DOCTOR HIRSCH: I just wanted to make sure  
3 we solved that because I heard it earlier.

4 ACTING CHAIR BORER: Are we satisfied with  
5 that?

6 MR. ROBY: The day one data was not  
7 reviewed by us. The ketoconazole review is in the  
8 clinical pharmacology section, page 111, and the only  
9 data is from day five, so the data presented now in  
10 day one is new to me.

11 DOCTOR HIRSCH: Why would that worry you?  
12 Suppose they only had day five data, what's wrong with  
13 that?

14 MR. ROBY: If cyclosporin steady state  
15 concentrations only were - sorry, bosentan steady  
16 state concentrations only were seen with cyclosporin  
17 then we would infer the same thing, that cyclosporin  
18 increases bosentan concentrations only twofold. We  
19 would have completely missed the 30-fold increase, and  
20 I'm not so sure that ketoconazole is a pure 3A4  
21 inhibitor only. It might also have some effect on  
22 transporters.

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1 DOCTOR HIRSCH: Oh, it definitely does,  
2 that's one of the reasons we don't consider it the  
3 perfect inhibitor anymore, but you now have data for  
4 that on days one and five, so it doesn't look like -

5 MR. ROBY: Until just a minute ago I have  
6 not seen that data.

7 DOCTOR HIRSCH: Well, whatever, let's  
8 assume that it's true for the moment, until we get our  
9 hands on it, that makes the cyclosporin thing rather  
10 mysterious to me.

11 MR. ROBY: Yes, absolutely.

12 DOCTOR HIRSCH: Because this drug does have  
13 both properties, and it's hard to explain why it  
14 didn't do anything much.

15 ACTING CHAIR BORER: Can you just give your  
16 name into the microphone?

17 MR. ROBY: I'm Gabriel Roby, Biopharm  
18 Review.

19 ACTING CHAIR BORER: Thank you.

20 DOCTOR HIRSCH: Jeff, you mean usually we  
21 would consider that an adequate work-up for a 3A4  
22 inhibitor, leaving aside the inducer and all that

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1 other complicated stuff, but that's more or less what  
2 we tell people to do, and, you know, you'd have to  
3 make what you will of a twofold increase, or it didn't  
4 look quite like twofold on there, but that would  
5 depend on the drug. I mean, a twofold increase of  
6 some kinds of things would worry you, but wouldn't for  
7 other things, so you make a decision. But, they seem  
8 to have tested that aspect of it, 3A4 inhibition.

9 So, I take it from this that the committee  
10 I general is satisfied to raise the questions, since  
11 there was an oral dose response that things that would  
12 affect plasma pharmacokinetics, that would also  
13 increase liver toxicity, were evaluated. I think we  
14 are happy then.

15 DOCTOR LINDENFELD: Yes.

16 DOCTOR HIRSCH: Personally, I'm still  
17 worried about why cyclosporin has such a big effect,  
18 and that seems worth pursuing.

19 ACTING CHAIR BORER: Okay.

20 I think that in summary we have some  
21 unanswered questions. We would suggest the FDA pursue  
22 the unanswered questions about drug/drug interactions

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1 based on metabolism by the CYP 450 system.

2 I'm on 3.4 now, Bosentan produced large  
3 increases in hepatic enzyme levels in a substantial  
4 number of subjects. Is it clear that hepatic toxicity  
5 is always reversible?

6 JoAnn?

7 DOCTOR LINDENFELD: I don't think it's  
8 clear that it's always reversible. It appeared to be  
9 reversible in the patients we saw, but there weren't  
10 large, large numbers of patients.

11 ACTING CHAIR BORER: Will instructions for  
12 frequent monitoring adequately address this risk?

13 DOCTOR LINDENFELD: I don't know if they  
14 will, as with other drugs, prevent occasional hepatic  
15 toxicity, but I think they'll help.

16 ACTING CHAIR BORER: Is there any other  
17 comment about that? Okay.

18 We'll get back to that when we get to the  
19 end here.

20 Bosentan produced substantial decreases in  
21 hematocrit in a substantial number of subjects. Is it  
22 clear that hematologic toxicity is always reversible?

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1 JoAnn?

2 DOCTOR LINDENFELD: I don't think it's  
3 clear that it's always reversible, again, because of  
4 the very small number of patients, but it appears that  
5 it is almost always reversible.

6 ACTING CHAIR BORER: Will instructions for  
7 frequent monitoring adequately address this risk?

8 DOCTOR LINDENFELD: I'm more comfortable  
9 here than with the hepatic toxicity that it will help  
10 prevent this, yes.

11 ACTING CHAIR BORER: Okay. We have  
12 unanimous agreement here.

13 DOCTOR ARMSTRONG: Could I just, Jeff,  
14 comment that I accept the sponsor's explanation based  
15 on work with nitrates and others that this is largely  
16 a dilutional problem, so the word hematologic toxicity  
17 strikes me as an unusual description of this issue,  
18 but, perhaps, I'm a sole dissenter.

19 DOCTOR LINDENFELD: I think we have some  
20 other worrisome data that this might be a hematologic  
21 toxicity. We are not certain, but it does depress  
22 raticula sites, and there's lots of other data, and

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1 I'm not at all comfortable with it purely being  
2 dilutional, given that we didn't see other dilutional  
3 effects in albumin or anything.

4 ACTING CHAIR BORER: As a practical matter,  
5 though, that doesn't seem to be a show stopper for us,  
6 if there's monitoring.

7 The development program in pulmonary  
8 hypertension is small, limiting its ability to uncover  
9 safety risks with incidence much below 1 percent. Are  
10 the safety data in the target population adequate to  
11 support approval?

12 JoAnn?

13 DOCTOR LINDENFELD: I believe they are  
14 adequate. They are not ideal, but I think that we've  
15 gotten the risk down to something that we're  
16 comfortable with.

17 ACTING CHAIR BORER: Okay.

18 So then, 3.6.2 becomes irrelevant.

19 Are there other safety issues?

20 DOCTOR LINDENFELD: The other safety issues  
21 are withdrawal, and I think we haven't seen anything  
22 that suggests there's a serious withdrawal problem.

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1 So, I don't believe there are other issues here.

2 ACTING CHAIR BORER: What about the  
3 populations who haven't been -- that haven't been  
4 studied, but, you know, presumably, would be potential  
5 candidates for getting this drug? Safety may or may  
6 not be different in those people, I guess, but the  
7 relation between benefit and risk might be. Should we  
8 say something about that patients with congenital  
9 heart disease, HIV patients, et cetera, et cetera,  
10 about the need for data for lack thereof?

11 DOCTOR LINDENFELD: I think there's a lack  
12 of data in congenital heart disease and certainly in  
13 HIV patients. I just don't think we have data. There  
14 were two congenital heart disease patients, I think  
15 that's lack of data.

16 ACTING CHAIR BORER: Okay.

17 Anybody else have any other safety issues  
18 they want to raise?

19 Mike?

20 DOCTOR ARTMAN: The other sort of  
21 subpopulation is those patients with connective tissue  
22 disease who had moderate or severe pulmonary fibrosis,

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1 and I don't know anything about how that was graded or  
2 measured, but those patients weren't studied.

3 ACTING CHAIR BORER: They were excluded,  
4 right.

5 DOCTOR FLEMING: Jeff, we did discuss the  
6 issue of early heart failure in the first three  
7 months, and the reason the sponsor chose the 62.5, I  
8 guess the question, given these folks and the  
9 potential for right heart failure and other issues,  
10 whether that is a safety issue reflected in the dosing  
11 strategy that needs to be articulated in the  
12 description.

13 ACTING CHAIR BORER: What do you think?

14 DOCTOR FLEMING: The answer is yes, I think  
15 that would be a sensible thing to do, based on the  
16 knowledge - the data I've seen.

17 ACTING CHAIR BORER: Okay.

18 Does anybody disagree with that? No.  
19 Okay, so that's another safety issue that requires  
20 some labeling mention.

21 4, subjects whose disease progressed  
22 despite randomized treatment went on to receive

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1 another drug, is it known that the benefits of the  
2 follow-on therapy are manifest after treatment with  
3 bosentan?

4 DOCTOR LINDENFELD: I don't think it's  
5 know, but we saw a very small amount of suggestive  
6 data that Flolan will still be beneficial in those  
7 patients. I don't really think we know, though, it  
8 was a very small numbers.

9 ACTING CHAIR BORER: Should we offer the -  
10 or we should we suggest the FDA to offer the sponsor  
11 some advice about the need to look at interaction  
12 between the different types of therapies that now are  
13 available? I mean, they act by different mechanisms,  
14 presumably, might be additive, might not be, might be  
15 competitive. Should we say something about that, and  
16 should these be studied together?

17 DOCTOR TEMPLE: Did the question mean in  
18 addition to, Ray, or after bosentan gets taken away?

19 ACTING CHAIR BORER: I'll tell you what I'm  
20 thinking, I'm thinking about in addition to. When one  
21 is taken away, of course we want to know, and we have  
22 some data, and presumably there will be more because

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1 it will happen, but I think that physicians, even  
2 though they are experts in the field, and those are  
3 the people who dispense these drugs, may want to give  
4 two drugs together that act by different mechanisms.  
5 And, I think we should know something about what  
6 happens when you do that.

7 Steve?

8 DOCTOR NISSEN: You know, it's always nice  
9 to know what happens when you combine therapies, but  
10 I think, you know, it's not something that we should  
11 suggest to the sponsor that they do. I think the  
12 medical community will probably address this in due  
13 course and we'll get some data, but I just, to me, it  
14 doesn't seem like the right thing to do.

15 ACTING CHAIR BORER: We've suggested it  
16 before when we knew it was likely to happen.

17 DOCTOR TEMPLE: Yeah, I mean, if you are  
18 hoping for a well-controlled trial that actually looks  
19 at the contribution of each component in the presence  
20 of the other, the medical community will not get you  
21 that information unless a drug company is urged to  
22 provide it. Now, people will use it, and they'll make

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1       their best guess, but formal good studies are mostly  
2       things drug companies do, unless NIH is interested.

3               ACTING CHAIR BORER: Can you use the  
4       microphone, sir?

5               DOCTOR RUBIN: Just for information, we are  
6       doing that. We've initiated a study comparing flolan  
7       plus placebo, versus flolan plus bosentan, for new  
8       patients who need to enter on to flolan therapy, to at  
9       least try to begin to address that question.

10              ACTING CHAIR BORER: Okay, well that's part  
11      of the information, that's for sure.

12              Ray, did you have a comment?

13              DOCTOR LIPICKY: Were you -- was this  
14      discussion an approvability issue, that is, you  
15      wouldn't approve until, or was this just idle chit  
16      chat?

17              ACTING CHAIR BORER: In my view, in my view  
18      it's not an approvability issue, but I think that to  
19      the extent that we don't have information about the  
20      combination, and I could conceive of people giving the  
21      combination, I think somebody ought to say in the  
22      label that we don't have any information about the

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1 combination.

2 DOCTOR LIPICKY: Okay.

3 DOCTOR HIRSCH: There is more than one  
4 combination available here now, it's been an amazing  
5 couple days.

6 ACTING CHAIR BORER: No, no, there's only  
7 one combination available now. There may be more  
8 after approvability letters are written, but they  
9 haven't been written yet.

10 Okay. Should bosentan be approved for the  
11 treatment of pulmonary hypertension?

12 JoAnn, why don't you answer that first?

13 DOCTOR LINDENFELD: Yes, I think it should  
14 be. I think we've seen a very clear beneficial  
15 effect, and while there are safety issues I think in  
16 this population, for the moment, those are manageable,  
17 and we should be collecting more data about those  
18 issues.

19 ACTING CHAIR BORER: Do you think the  
20 company should be encouraged by the FDA in its most  
21 encouraging manner to look at lower doses?

22 DOCTOR LINDENFELD: I think that would be

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1       terrific, to know that a lower dose with less toxicity  
2       might be beneficial.

3                ACTING CHAIR BORER: Okay.

4                Let's go down the table, because the  
5       voting requirements now are that we all verbalize our  
6       vote, starting with Alan.

7                DOCTOR HIRSCH: Approve.

8                DOCTOR ARMSTRONG: Enthusiastic yes.

9                ACTING CHAIR BORER: Tom?

10               DOCTOR FLEMING: Yes, it should be  
11       approved, and I'm assuming that automatically the  
12       post-marketing surveillance will be underway to be  
13       able to assess if there are risks of pulmonary hepatic  
14       failure, et cetera.

15               ACTING CHAIR BORER: Automatically if you  
16       say it should be.

17               DOCTOR FLEMING: So, you're saying we  
18       wouldn't - we can't presume that we will have a  
19       reporting of cases of pulmonary hepatic failure?

20               ACTING CHAIR BORER: Oh, I think if it's  
21       spontaneous reporting we are talking about we can  
22       assume there will be some spontaneous reporting, but

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1 unless -

2 DOCTOR HIRSCH: If you are going to change  
3 the questions as you go down the line, you're going to  
4 have to do two sets of questions.

5 ACTING CHAIR BORER: Sorry?

6 DOCTOR HIRSCH: You have to ask us all the  
7 same questions.

8 ACTING CHAIR BORER: Oh, okay. Well, we'll  
9 go back and we'll get those questions back.

10 DOCTOR FLEMING: So, let me stick to it as,  
11 yes, approve.

12 ACTING CHAIR BORER: Okay. We'll get back  
13 to the post-marketing issue.

14 I vote to approve as well, but I'm going  
15 to add the comment, I will second JoAnn's comment  
16 about the need to look at lower doses.

17 Doctor Brem?

18 DOCTOR BREM: I vote to approve, and I  
19 concur with your view of looking at lower doses. I  
20 think that would be very helpful.

21 ACTING CHAIR BORER: Steve?

22 DOCTOR NISSEN: Yes, clearly a major

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1 therapeutic advance, kind of a landmark in the  
2 treatment of this disease, and I vote for approval of  
3 the 62.5 mg dose progressing to 125, and 62.5  
4 progressing to 250.

5 ACTING CHAIR BORER: Okay.

6 Doctor Anderson?

7 DOCTOR ANDERSON: Yes. I think this is an  
8 expression of a sensitivity to an urgent need to  
9 develop drugs that will reduce the dependence on the  
10 mechanical devices that are now being used by the  
11 patients who have to rely on em, and I certainly vote  
12 yes.

13 I would strongly urge the sponsors to give  
14 some attention to the various risks that apparently  
15 are associated with the drug, and to ensure that there  
16 are no real problems, no unnecessary problems, created  
17 in addition to those problems.

18 ACTING CHAIR BORER: Doctor Artman?

19 DOCTOR ARTMAN: I vote to approve.

20 ACTING CHAIR BORER: Okay.

21 We are not done, because Alan pointed out  
22 that he wanted an opportunity to answer the other

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1 question individually.

2 Is there some mandate that we want to make  
3 for post-marketing, a formal post-marketing study?

4 DOCTOR HIRSCH: Well, you raised the  
5 question, we don't have to start on my end, but there  
6 is that question we've all day long been asking, so  
7 start on that end.

8 ACTING CHAIR BORER: Okay.

9 Michael?

10 DOCTOR ARTMAN: What's the question?

11 DOCTOR HIRSCH: Do you feel that the  
12 advisory panel should mandate a post-marketing  
13 surveillance of hepatic toxicity to provide a better  
14 estimate of this toxicity, also to be used in other  
15 prospective trials?

16 DOCTOR ARTMAN: Yes, I do.

17 ACTING CHAIR BORER: Did you want to expand  
18 on that, Tom?

19 DOCTOR FLEMING: I had made an assumption,  
20 and Jeff modified my -- my assumption was, in this  
21 setting, with patients as carefully monitored as they  
22 are, with pulmonary hepatic failure being such a

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1 critically serious event, that it would automatically  
2 be reported, is that an unfair assumption?

3 DOCTOR ARTMAN: Yes, I think that is an  
4 unfair assumption.

5 DOCTOR FLEMING: So, essentially, to ensure  
6 then that that would be reported we would actually  
7 have -- we would have to suggest, at a minimum, there's  
8 passive surveillance, active surveillance?

9 Bob, what is the --

10 DOCTOR TEMPLE: Well, the most obvious  
11 thing they could do would be to register patients.  
12 That wouldn't be hard, given the community, and it  
13 would allow you to then probe the registry and ask  
14 people whether there is this experience.

15 If you just wait for them to come in, I'm  
16 quite confident that they will for the most part. We,  
17 you know, we discovered the hepatotoxicity of  
18 bromfinac within two months, and people who need a  
19 transplant go to a certain number of centers, but it's  
20 not really the same as having a full complete census.  
21 So, that's what we might do if are worried about that,  
22 we might ask them to register the patients. They

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1        might want to do that anyway, I don't know, for all I  
2        know you are planning that already. I don't know.

3                DOCTOR KORBIN: Yes, we are going to put in  
4        place a very comprehensive program on this issue.

5                DOCTOR FLEMING: The other reason to do  
6        that, of course, is you are very interested in  
7        pregnancies and exposures, so there's more than one  
8        thing that you'd learn from having track of everybody.

9                DOCTOR HIRSCH: With the new chemical  
10        entity, really, at this point, and we're opening up a  
11        wonderful arena of cardiovascular pharmacology, I do  
12        think that beyond your good intentions it is, I think,  
13        my intent from the panel to assure that that data is  
14        collected.

15               DOCTOR FLEMING: So, I'm interpreting your  
16        answer, Bob, to be, yes, that in all likelihood we  
17        would get this information, it would show up, it would  
18        be reported, but for more global reasons a registry  
19        would be advisable.

20               DOCTOR TEMPLE: Yes, you know, you could -  
21        there's a range of questions you might think of asking  
22        if you had access to the patient population. So, we

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1 would need to explore with them what kind of registry  
2 there might be. I mean, you know, you could look at  
3 long-term testicular effects, too, possibly, and  
4 there's a lot one might gain. You could also look at  
5 liver tests that didn't lead to anything terrible, how  
6 many people are discontinuing in the real world. So,  
7 there are things one might do with access to that kind  
8 of data.

9 DOCTOR KORBIN: If you would like, we can  
10 show you what we are planning to put in place.

11 ACTING CHAIR BORER: I'm sorry?

12 DOCTOR KORBIN: Would you like to see what  
13 we are planning to put in place? We have one slide on  
14 this issue, to show you exactly how we want to do  
15 this?

16 ACTING CHAIR BORER: Sure.

17 DOCTOR KORBIN: Simon?

18 MR. BUCKINGHAM: My name is Simon  
19 Buckingham, I'm President of Actelion for the U.S.

20 If I could have slide 498, 499, it's  
21 changed, okay. Clearly as a company, we take this  
22 issue very, very seriously, and recognize that

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1 monitoring is an absolute must, and that the labeling  
2 must contain clear warnings and clear guidelines for  
3 physicians, but also both patient and physician  
4 education is very important to us.

5 One of the models and plans that we are  
6 discussing at the moment, and have planned internally  
7 but have not yet discussed with the FDA, is to create  
8 a central call-in system for all physicians who wish  
9 to initiate treatment with bosentan. That would go  
10 through an independent third party central  
11 clearinghouse to create a patient, and if you like,  
12 physician database of who is on the drug, what their  
13 demographics are, and who is using it. And, through  
14 a limited network of specialty pharmacies, the drug  
15 would be distributed directly to patients. That would  
16 offer the opportunity to ship drug directly to  
17 patients with liver monitoring reminders going monthly  
18 to patients, so that whenever they get the drug they  
19 are reminded about the liver monitoring. It can also  
20 be utilized to follow up any discontinuations and  
21 follow up any adverse event reporting.

22 At the same time to physicians involved in

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1 the program, it can be a heightened awareness of  
2 spontaneous adverse event reporting, as well as liver  
3 monitoring reminders.

4 ACTING CHAIR BORER: Steve?

5 DOCTOR NISSEN: Was your intention to make  
6 that database available to the FDA?

7 MR. BUCKINGHAM: It would certainly be  
8 available to the FDA.

9 ACTING CHAIR BORER: Okay.

10 I think what you've heard is that the  
11 sense of the committee, if I'm understanding  
12 correctly, is that the FDA should encourage that this  
13 should be done, and should have the data made  
14 available to it.

15 Okay. Ray, is there anything else that  
16 you want us to discuss?

17 DOCTOR LIPICKY: No, you are fine.

18 ACTING CHAIR BORER: Unless anybody else on  
19 the committee has any other comment, we're adjourned.

20 (Whereupon, the meeting was concluded at  
21 1:00 p.m.)  
22

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CERTIFICATE

This is to certify that the foregoing transcript in the  
matter of: Meeting of the Cardiovascular and Renal  
Drugs Advisory Committee

Before: DHHS/PHS/FDA/CDER

Date: August 10, 2001

Place: Bethesda, MD

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
typewriting.

  
A handwritten signature in cursive script, appearing to read "K. M. F. H.", is written over a horizontal line.